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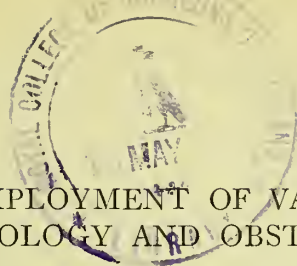
REPORT ON THE EMPLOYMENT OF VACCINE THERAPY IN GYNECOLOGY AND OBSTETRICS

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REPORT ON THE EMPLOYMENT OF VACCINE THERAPY IN GYNECOLOGY AND OBSTETRICS¹

By J. WHITRIDGE WILLIAMS, M. D., EDWIN B. CRAGIN, M. D., AND FRANKLIN S. NEWELL, M. D.

BEFORE beginning its report, your committee desires to express its conviction that its members were unfortunately selected, as none of us has worked upon the scientific side of the subject, and one of us, at least, has had no experience in the practical employment of vaccine therapy.

For this reason we are unable to express an authoritative opinion as to its merits derived from personal experience, and are therefore obliged to base our report upon a critical study of the literature of the subject. With this object in view, Dr. Cragin reviewed the publications dealing with gonorrhœal infections, Dr. Newell those upon infections of the urinary tract and of the internal genitalia, and Dr. Williams those upon puerperal infection and the more general aspects of the entire subject. The report therefore represents the joint work of the three members of the committee and is concurred in by each of them. It is unnecessary to state that the subject was approached with an open mind and that our judgment, as far as possible, is unprejudiced and objective.

After a few general remarks concerning opsonins and vaccines, we shall consider the use of the latter in the treatment of the following conditions:

1. Gonorrhœal infections, including vulvovaginitis in little girls.
2. Infections of the urinary tract.
3. Inflammatory conditions of the internal genitalia.
4. Puerperal infections, and finally we shall summarize our conclusions in a few sentences.

Following the ingenious work of Metchnikoff, which began in 1865, it has become recognized as a well established fact that the leucocytes and other cells take up into their interior, foreign bodies and bacteria, which then undergo various changes which may eventually result in their destruction. The process is known as phagocytosis, and it is apparent that if all the bacteria concerned in the production

of a disease could be destroyed in this way the process must come to an end.

This view was promptly accepted, particularly in France, and, with various modifications and amplifications, became the basis for the cellular theory of immunity. In Germany on the other hand, the establishment of immunizing processes was attributed to the presence or development of certain substances in the blood serum or tissue juices, independent of the leucocytes, and has led to the development of the humoral theory of insanity.

For many years the differences between the supporters of the two doctrines were apparently irreconcilable; and it was not until Sir Almroth Wright enunciated his views concerning opsonins and vaccine therapy that either side frankly admitted that each theory was based upon accurate observations and was entitled to careful consideration. Wright's publication directed particular attention to the practical application of the doctrines of immunity, and since his lectures in this country in 1907 opsonic or vaccine therapy has been a very live issue.

For many years it has been known that one of the first responses to infection is an increase in the number of leucocytes — leucocytosis. In localized infections the process is practically limited to the infected area, around which the leucocytes form a wall of varying thickness, which serves partly as a means of removing the bacteria, but more particularly as a filter which tends to prevent their spreading into the rest of the organism. In abscess formation there is an extensive migration of leucocytes to the affected area, and at first they take up large numbers of bacteria, but later, as the result of insufficient nutrition and possibly also of certain products of the bacteria themselves, they begin to break down when the tryptic ferment contained in them causes still further liquifaction of the tissues and gives rise to a typical abscess.

Metchnikoff, Wright, and others pointed out

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that in many of the ordinary infections, which are undergoing recovery, there is a marked increase in the extent of phagocytosis; and the latter holds that the increased ability to devour the bacteria is in great part due to the presence in the blood serum and tissue juices of substances which so sensitize the former that they can be more readily ingested by the leucocytes, while at the same time their other properties are not affected. These substances Wright designated as opsonins — from *opsono*, I prepare for food, or cater to, and, as they become more abundant during recovery or convalescence from disease, must be regarded as an essential factor in the production of active immunization.

By the term active immunity we understand the phenomena accompanying spontaneous recovery from an infectious disease and which for a time at least prevent a new attack; as well as similar changes resulting from the artificial injection of small quantities of the specific micro-organism or toxin into the tissues of the individual. Such a response must be regarded as nature's effort to rid the organism of the offending bacteria and their products. Increased phagocytosis, however, is only one of the factors concerned, and other complicated bodies are also produced which lead to the clumping, solution, and absorption of the bacteria and their toxic products, namely, the agglutinins, lysins, and other bactericidal substances.

In passive immunity, on the other hand, the toxins which characterize the disease are simply neutralized or rendered inert by the injection into the individual of protective substances, which have developed in the serum of another individual as the result of active immunization. This form of immunity should therefore be regarded merely as a temporary expedient, which simply serves to hold the disease processes in check sufficiently long to permit nature to manufacture and bring into play such protective and bactericidal substances as will rid the individual of the offending bacteria and their toxins. Active immunization on the other hand is more permanent in its effect, and when well developed not only copes with the existing infection, but affords a longer or shorter guaranty against its recurrence.

It would lead us too far to consider these phenomena in detail, and it suffices here to state that the opsonins are simply one of the protective substances developed in the body fluids, and that it has not yet been determined whether they correspond to the ordinary amoebocytes or are of some other nature. In any event, as has already been indicated, they do not kill or cause solution of the bacteria, but simply sensitize them for ingestion by the leucocytes. It is generally believed that there are various categories of opsonins, each of which is specific in its action; thus a given serum may be rich in opsonins for the tubercle bacillus and lacking those for the streptococcus or colon bacillus.

Wright's great contribution to the chapter of immunity was the recognition of the existence and mode of action of opsonins, as well as the invention of a method for determining the extent to which they are present. The latter is effected by means of the opsonic index. This indicates the quantity of a specified variety of bacterium which will be taken up by a given number of phagocytes in the serum of the individual to be tested, as compared with those devoured by the same number of phagocytes in the presence of a similar quantity of serum from a normal person.

The technique for such determinations is quite complicated and gives reliable results only in the hands of expert and trained investigators. It consists in principle, however, of mixing one part of the serum of the individual to be tested, with equal parts of washed leucocytes, and of a suspension of the bacteria in question, placing the mixture in a thermostat for 15 minutes, making a smear and counting the number of bacteria ingested by 100 leucocytes, and then comparing the results with those obtained in a similar experiment in which the serum previously employed is replaced by that of a normal person. The opsonic index is expressed by a fraction in which the results obtained in the former experiment form the numerator and those obtained in the latter the denominator. In order to avoid complicated figures, it is customary to designate the latter as unity, and to express the former by a decimal fraction. Thus if 242 bacteria were counted in the preparation made

from the patient's serum and 186 in the control, the index would be 121-93 or 1.30.

The term vaccine, which was originally employed to designate the material obtained from cowpox and used for protection against smallpox, was extended by Pasteur to the injection of any bacterial culture or toxin into another animal for the purpose of preventing or curing disease. Since his time this has been done to a very considerable extent, and Wright conceived the idea that the employment of vaccines could be considerably extended and regulated by using the opsonic index as a guide for their administration. He held that under normal conditions the opsonic index should be 1; whereas in infections in which the patient is responding satisfactorily it should be higher, while in those in which recovery is not occurring it should be less than normal. Consequently the existence of a low opsonic index against a given micro-organism indicates that the latter is the cause of infection and that the patient is not reacting to it.

Under such circumstances he advanced the theory that the injection into the subcutaneous tissues of a definite quantity of the offending bacteria, which had been previously killed by heat, would result in a further stimulation of the immunizing processes and thus favor or hasten cure. Ordinarily, he noted that the injection of a certain number of millions of dead bacteria would be followed by a decided reaction on the part of the patient, as well as by a temporary but considerable decrease in the opsonic index. This drop, which he designated as the negative phase, is ordinarily of short duration and is soon followed by a rise of the index above 1. As long as it remains elevated no further injections are necessary, but as soon as it begins to decrease and approaches unity, a further injection should be given. The number of vaccinations necessary to effect a cure varies markedly in different infections, as well as the number of bacteria injected, and the latter may vary from 5 or 10 up to 500 or even 1,000 millions.

When one considers the rationale of such treatment, it would appear a priori that it would probably be more useful as a prophylactic than as a therapeutic measure. Thus, if small quantities of the killed bacteria are

injected into a normal individual an immunizing response might be obtained, which would simulate that occurring in recovery from spontaneous infections, and thus afford immunity against subsequent attacks. This has been done with greater or less success as a prophylactic measure against plague, cholera, typhoid fever, and dysentery, and the results obtained prove that it is a rational and scientific procedure.

On the other hand in the actual treatment of existing disease, the method does not at first glance appear so rational; as it would seem somewhat paradoxical to introduce more bacteria into an individual who is already suffering from the effects of their presence. Moreover, practical experience indicates that the effect will differ materially according as the infection is localized or general. Wright has offered an apparently satisfactory explanation of the *modus operandi* in localized infections, particularly when due to the tubercle bacillus or the staphylococcus. In such conditions, he assumes that the bacteria are limited to the local lesion, and are shut off from the general organism by the leucocytic wall and inflammatory tissues by which it is surrounded. Consequently they do not gain access to the general circulation and are thus unable to produce an immunizing response. Whereas, when the vaccine is injected, opsonins are formed in the serum and body juices which then gain access to the infected area and prepare the bacteria for ingestion by the leucocytes. The favorable results obtained in this variety of infections apparently indicate that the theory is in essential accord with the facts.

On the contrary, vaccination would at first glance appear to be thoroughly irrational in generalized infections; as in such cases large numbers of bacteria are circulating in the blood and should apparently be able to call forth any immunizing response of which the organism is capable. It would, therefore, seem that the individual who is suffering from the presence of bacteria and their toxins would only be damaged still further by the introduction of a greater quantity into his system. Wright, however, contends that in such cases the opsonins are not developed in the blood serum, but rather in the juices of the subcu-

aneous tissue into which the vaccine is injected, and that their formation may be sufficient to turn the tide and enable the patient to recover. Satisfactory proof of the correctness of this explanation has not yet been adduced, while the uncertain and unfavorable results following the employment of vaccine therapy in generalized infections seem to indicate that it may never be substantiated.

Since the development of these theories, opsonic determinations have been made in a large number of diseases, and their cure has been attempted by means of vaccines, as is well reviewed in the recent articles of Thomas and Tileston. How satisfactory the results have been in gynecological and obstetrical work will be shown in the following pages; although it would seem that the therapeutic application of vaccines has been more generally recognized than the practical value of the determination of the opsonic index. Wright and his followers believe that scientific vaccine therapy is possible only when controlled by frequent determinations of the index, although in the hands of most observers, such as Fitzgerald, Whitman and Strangeways, Cole, Moss, and the majority of German investigators, its technique has been found to be so difficult, and such variable results have been obtained, that the general tendency is to regard it rather as a scientific demonstration of the existence of opsonins than as a practical guide for prognosis and treatment.

After this brief review of the theoretical aspects of the subject we shall now consider the practical results following the use of vaccine therapy in gynecological and obstetrical work.

1. *Gonorrhæal infections.* Vaccines have been extensively employed in various forms of gonorrhæal infection, and the most satisfactory results appear to have been obtained in the treatment of chronic gonorrhæal arthritis and of chronic vulvo-vaginitis of little girls. Cole and Meakins in 1907 reported the results obtained in 20 cases of the former, and found that a certain number of patients improved much more rapidly and satisfactorily than under the usual methods of treatment. At the same time they stated that the variations in the opsonic index were so great as to render

it of very questionable value as a guide to treatment. Similar observations were made by Irons, Eyre and Stewart, and Hartwell, and their consensus of opinion, based upon a total of 127 cases, is that in many chronic cases symptomatic cure can be effected in a shorter time than with any other method of treatment. Such results however, do not necessarily imply that the gonococci were destroyed, as in several instances their presence was demonstrated at operation, months after the disappearance of subjective symptoms.

According to Allen, Stropshire, Hartwell, and other observers, gonococcus vaccines are practically valueless in the treatment of acute urethritis, and the only author giving a favorable report is Stephens. On the other hand, somewhat more favorable results were reported in chronic cases by Allen, Bosanquet and Eyre, Laxton, and others, but even here only a small proportion of the patients were really cured.

Good results have been reported in the treatment of several cases of general gonococcus septicæmia, although in Dieulafoy's two patients gonococci could be cultivated from the blood long after the disappearance of all symptoms.

Generally speaking it may be said that vaccines exert a very favorable influence upon the course of chronic vulvo-vaginitis in little girls, and series of cases have been reported by Churchill and Soper, Butler and Long, Hamilton and Cook, Thomas, and Hamilton. In several of them equal numbers of patients were treated alternately by means of vaccines and by the usual antiseptic methods; and the general consensus of opinion is well summarized in the conclusions of Butler and Long: "We believe it no exaggeration to state that vaccine therapy has a place in the treatment of gonorrhœa in the female, that it appears to be far more efficient and at the same time scientifically more tenable than local antiseptic treatment."

Possibly the most conclusive demonstration of its utility has been adduced by Hamilton, who reports the results obtained in 344 patients observed in the Vanderbilt clinic. He states that in 260 patients treated by irrigation with various antiseptic solutions 60 per cent of cures

resulted after an average duration of 10.1 months of treatment; whereas 90 per cent of the 80 patients treated by vaccines were cured after an average treatment of 1.7 months. Even in this the most favorable series thus far reported, vaccine therapy did not give universally good results, as a certain proportion of cases failed to receive any benefit from it.

Contrary to the general experience in other infections, the general opinion seems to indicate that in this condition almost as satisfactory results may be obtained by the employment of stock vaccines as by those prepared from organisms cultivated directly from the patient. On the other hand, one should bear in mind the possibility that in some of the cases in which no reaction occurred the vaccine employed was inert.

2. *Infections of the urinary tract.* Series of cases comprising the various inflammatory conditions of the bladder, ureter, and renal pelvis due to various bacteria have been reported by Lenhart, Dodge, Rovsing, and Hartwell and Streeter. In the majority of cases the infection was due to the colon bacillus, which was noted in forty-one of the 60, and in twelve of the 19 cases reported by Dodge, and Hartwell and Streeter respectively. In such conditions, no matter what the infecting organism may be, stock vaccines are useless; but in the milder cases of colon infection autogenous vaccines are sometimes efficient in that they bring about symptomatic cure, but rarely lead to the total disappearance of the bacteria from the urine. It may be stated that somewhat better results are obtained in pyelitis than in cystitis, although the possibility of drawing definite conclusions in this regard is rendered difficult by the fact that the majority of the patients had been subjected to medicinal and surgical treatment, as well as to vaccine therapy.

Geraghty, after reviewing the subject in 1909, stated that the evidence thus far available would seem to indicate that vaccines are useless in streptococcus infections, but possess a certain value in the treatment of those due to the colon bacillus.

In addition to the larger series just mentioned, isolated cases have been reported by Leary, Francioni, White and Eyre, Butler,

Schmidt, Cunningham, Briscoe, Billings, Belfield, and others. In some patients symptomatic cure resulted, while in others the vaccines appeared to exert no effect upon the condition; but even the most enthusiastic advocates of their employment admit that the bacteriuria usually persists.

As far as we have been able to ascertain, French and Routh are the only authors who have thus far employed vaccines in the treatment of the pyelonephritis of pregnancy. In each instance symptomatic cure resulted, but bacteria persisted in the urine until after delivery, when the process gradually cleared up. From the evidence at present available, it would seem permissible to conclude that the results following vaccine therapy in the pyelitis and pyelonephritis of pregnancy are practically identical with those obtained by rest in bed and the administration of salol or urotropin, as in both symptomatic cure results, but the bacteriuria persists until after the termination of pregnancy.

3. *Infection of the generative tract.* Wright and Harris have reported good results following the administration of autogenous colon vaccines in certain cases of endometritis complicated by cervical catarrh. In numerous instances, however, the amount of the discharge was merely diminished, and a definite cure was not effected until after the patient had been curetted.

Hoobler, Leary, and Oastler have also reported cases in which chronic pelvic inflammation persisted after operation, and was complicated by prolonged suppuration and the development of fistulous tracts. In several instances, no matter whether the lesion was due to the streptococcus, colon bacillus, or to mixed infections, the condition gradually cleared up after the repeated administration of suitable vaccines. Whether such results were post hoc or propter hoc it is impossible to say, as accurate conclusions cannot be drawn from the few cases thus far reported. Similar treatment was employed by Oastler, and Hartwell, Streeter and Green in certain chronic peritoneal infections, broken down laparotomy wounds and sluggish sinuses. They reported fairly satisfactory results, and it is possible that such conditions may afford a field for the more ex-

tensive employment of vaccine therapy in the future.

Moreover, it is interesting to note that Lerda and Ritchie have attempted in certain operative cases to diminish the possibility of infection by vaccinating the patient prior to resorting to surgical procedures. Their results however, were not sufficiently encouraging to make it likely that they will find many imitators.

4. *Puerperal infection.* The greater part of the work thus far reported in this condition has consisted in attempting to ascertain the diagnostic and prognostic value of the opsonic index in normal pregnant and puerperal women, as well as in the presence of infection; while a comparatively small number of observers have reported the results following the employment of vaccines in the treatment of the latter condition.

Eisler and Sohma studied the opsonic index in rabbits and guinea pigs, which had been immunized to streptococci, and found that opsonins were not transmitted to the foetus in utero, but readily passed over in the maternal milk.

Series of opsonic determinations have been made in pregnant and puerperal women by Koessler and Neumann, Heynemann and Barth, Gugigsberg, Cathala and Lequeux, Martin, Robbers, and Much. With the exception of the last two, all of these investigators concluded that such determinations were so difficult and gave such variable results that the opsonic index was practically of little value either in the diagnosis or treatment of infectious conditions occurring during pregnancy or the puerperium. Much, however, believed that useful results might be obtained, while Robbers found that repeated determinations were necessary to justify a definite conclusion and, before it has reached, the diagnosis would have been established by the usual bacteriological methods.

Koessler and Neumann made the interesting observation that the opsonic index for the tubercle bacillus was normal in only 48 per cent of puerperal women, as compared with 87 per cent in other normal individuals. They, therefore, concluded that in such patients the resistance to tuberculosis was lowered, and that the condition offered an explanation for the

ravages which it made when developing or flaring up during the puerperium.

Before considering the therapeutic value of vaccine therapy in puerperal infection, it may be stated that in the ordinary local infections, no matter to what variety of bacteria they may be due, the natural tendency is toward recovery, and consequently specific treatment is usually unnecessary. On the other hand, when the process passes beyond the uterus, it rapidly gives rise to peritonitis or general infection — conditions which are so serious that any efficient means of treatment would prove a great benefaction. In such cases the infecting micro-organism is usually the streptococcus, staphylococcus aureus or colon bacillus, either alone or in combination, and the question, therefore, resolves itself into the possibility of combatting the resulting peritonitis or general infection; as the short time necessary for invasion by highly virulent bacteria makes impossible any attempt to jugulate the original local infection by the comparatively slowly acting vaccines.

Moreover, in view of the fact that all of the bacteria concerned are subject to marked variations, it is imperative, if satisfactory results are to be obtained, to employ autogenous rather than stock vaccines. Unfortunately, their preparation necessitates still further delay, so that the fate of the patient is usually sealed before the first injection of autogenous vaccine can be administered. For these reasons, the prospect for successful vaccine therapy in the acute generalized infections does not appear encouraging; and Sir Almroth Wright informed one of the members of the committee last autumn that he held the same opinion, and that favorable results could be expected only in the more chronic cases.

On surveying the literature we find that comparatively few cases of streptococcus infection have been reported, although Wright in 1907 stated that vaccine therapy had been employed in six cases of streptococcus endocarditis with four deaths, three of the patients showing a distinct immunizing response, which was absent in the others. Allen in 1908, likewise, considered the results fairly satisfactory and referred to the cases of Sutcliffe and Bayly, Harris, Barr, Bell and Douglas, but the more recent reports have not been encouraging. Weaver and Tunnicliffe likewise reported sat-

isfactory results in chronic streptococcal otitis media following scarlet fever, as well as in certain cases of erysipelas.

Isolated cases of puerperal infection have been treated by vaccines by Jewett, Turton, Crowe and Wynn, Wilson and Oastler, while a series of 18 cases was reported by Hartwell, Streeter and Green.

Careful study of the histories of these patients has failed to convince us that the vaccines have exerted any marked effect upon the course of the disease, while in several instances we received the impression that recovery would have resulted no matter what line of treatment had been adopted. The only authors who have thus far reported a considerable series of cases are Hartwell, Streeter, and Green. They treated 18 patients by vaccines in conjunction with the usual medical and surgical methods of treatment, and stated that streptococci were demonstrated once in the four instances in which blood cultures were made. All of the patients recovered, and in eleven the authors believe that repeated vaccinations had some effect upon the course of the disease, while in the others it appeared to be without effect. The fact, however, that in a number of cases vaccination was repeated many times at intervals of several days, would seem to indicate that the infection, if really generalized, pursued a chronic course. Tileston, however, in his recent review of the entire subject considers that their results were at least encouraging enough to lead to further trial.

Rosenthal, Heynemann and Barth, Gugigberg, and others have concluded that this method of treatment offers no prospect of cure in acute infections, although they admit that it may possibly be of value in certain chronic cases. On the other hand, Meakins believes that he has obtained good results in acutely infected rabbits and thinks that the outlook is promising.

After this survey of the literature it seems safe to conclude that vaccine therapy has as yet been employed in so few cases of puerperal infection that it is impossible to express a definite opinion as to its merits. At the same time it would appear that the greatest prospect for its successful use is in chronic local infections, and that it offers very little hope in acute general infections where aid is so urgently needed.

We would suggest that it is advisable to continue work along these lines, and that large series of cases should be treated with careful bacteriological control, every alternate patient receiving the vaccine and the other being left alone, or, if subjected to local treatment, care should be taken that it be identical with that employed in the vaccine cases, so that with the exception of the use of the vaccine all conditions will be as nearly alike as possible. If under such conditions a radical difference can be noted in the behavior of the two series, it would be permissible to attribute it to the treatment. Only in this way will it be possible to draw tenable conclusions; as we hold that those drawn from isolated cases are absolutely valueless, and even large series of cases which are not controlled can prove but little, as under such conditions it is impossible to exercise critical judgment, and it may well happen that conclusions may be drawn, which further investigation will show to be fallacious.

CONCLUSIONS

The evidence at present available seems to justify the following tentative conclusions concerning the value of vaccine therapy in gynecology and obstetrics.

1. Opsonins undoubtedly play a part in the production of active immunity. On the other hand the determination of the opsonic index is technically very difficult and is subject to such variations that it is not available as a diagnostic or prognostic guide, and even among trained bacteriologists there is considerable skepticism as to its practical value.

2. Immunization by means of vaccines is a well established prophylactic measure against certain infectious diseases, notably typhoid, cholera, plague, and dysentery. Vaccine therapy is undoubtedly a valuable remedial agent in local infection due to the tubercle bacillus or the staphylococcus, less so in local infections due to other pathogenic bacteria, while there is considerable doubt as to its efficiency in acute general infections.

3. In chronic gonorrhœal arthritis and urethritis it is a valuable adjunct to other treatment and occasionally may lead to cure alone. It appears to be useless in the acute infections, while it is more efficient in the treatment of

the vulvo-vaginitis of children than any other means, but even here it does not always result in cure.

4. In infections of the urinary tract, especially those due to the colon bacillus, it sometimes results in symptomatic cure, but rarely relieves the bacteriuria. The scanty reports concerning the pyelitis and the pyelonephritis of pregnancy, indicate that vaccine therapy is no more efficient than the usual treatment by rest in bed and the administration of salol or urotropin, as in neither does the bacteriuria disappear until after the termination of pregnancy.

5. In certain cases of endometritis, it appears to reinforce the curative influence of curettage. The reports concerning its use in pelvic inflammatory diseases are too scanty to justify conclusions, but it would seem that it may be

of value only in chronic post-operative cases with sluggish fistula formation.

6. As the ordinary localized puerperal infections, irrespective of the nature of the offending bacteria, tend to spontaneous cure, the field for vaccine therapy is practically limited to acute general infections where it unfortunately appears to be of little value, and the most that can be said from the reports thus far available is that its employment does no harm.

Further research in this direction is desirable, and definite conclusions can be drawn only after the observation of large series of cases, with careful bacteriological diagnosis, in which every alternate patient is treated with autogenous vaccines, while the others are left alone, or at most subjected to such general treatment as is common to both series of cases.

